GENE THERAPY FOR EFFECTOR CELL REGULATION

CROSS-REFERENCE TO RELATED APPLICATIONS

The present application is a continuation-in-part of U.S. patent application Ser. No. 08/446,918 for "Gene Therapy for T Cell Regulation", filed May 18, 1995, U.S. Pat. No. 5,705,151 incorporated herein by this reference in its entirety. The present application is also a continuation-in-part of U.S. patent application Ser. No. 08/484,169 for "Mycobacterium Peptides, Nucleic Acid Molecules, and Uses Thereof", filed Jun. 7, 1995, now abandoned, incorporated herein by this reference in its entirety.

FIELD OF THE INVENTION

The present invention relates to a product and process for regulating T cell activity by providing a superantigen gene, in the presence or absence of a cytokine and/or chemokine gene. The present invention also relates to a product and process for regulating T cell activity by providing a peptide and a superantigen gene, in the presence or absence of a cytokine and/or chemokine gene. In particular, the present invention relates to a product and process for controlling tumor development, immune responses to infectious diseases and diseases caused by immunological disorders.

BACKGROUND OF THE INVENTION

Two major causes of disease include infectious agents and malfunctions of normal biological functions of an animal. Examples of infectious agents include viruses, bacteria, parasites, yeast and other fungi. Examples of abnormal biological function include uncontrolled cell growth, abnormal immune responses and abnormal inflammatory responses. Traditional reagents used attempt to protect an animal from disease include reagents that destroy infectious agents or cells involved in deregulated biological functions. Such reagents, however, can result in unwanted side effects. For example, anti-viral drugs that disrupt the replication of viral DNA also often disrupt DNA replication in normal cells in the treated patient. Other treatments with chemotherapeutic reagents to destroy cancer cells typically leads to side effects, such as bleeding, vomiting, diarrhea, ulcers, hair loss and increased susceptibility to secondary cancers and infections.

An alternative method of disease treatment includes modulating the immune system of a patient to assist the patient's natural defense mechanisms. Traditional reagents and methods used to attempt to regulate an immune response in a patient also result in unwanted side effects and have limited effectiveness. For example, immunosuppressive reagents (e.g., cyclosporin A, azathioprine, and prednisone) used to treat patients with autoimmune disease also suppress the patient's entire immune response, thereby increasing the risk of infection. In addition, immunopharmacological reagents used to treat cancer (e.g., interleukins) are short-lived in the circulation of a patient and are ineffective except in large doses. Due to the medical importance of immune regulation and the inadequacies of existing immunopharmacological reagents, reagents and methods to regulate specific parts of the immune system have been the subject of study for many years.

Stimulation or suppression of the immune response in a patient can be an effective treatment for a wide variety of medical disorders. T lymphocytes (T cells) are one of a variety of distinct cell types involved in an immune response. The activity of T cells is regulated by antigen, presented to a T cell in the context of a major histocompatibility complex (MHC) molecule. The T cell receptor (TCR) then binds to the MHC:antigen complex. Once antigen is complexed to MHC, the MHC:antigen complex is bound by a specific TCR on a T cell, thereby altering the activity of that T cell.

The use of certain staphylococcal enterotoxin proteins that are capable of complexing with MHC molecules to influence T cell function has been suggested by various investigators, including, for example, White et al., *Cell* 56:27–35, 1989; Rellahan et al. *J. Expt. Med.* 172:1091–1100, 1990; Micusan et al., *Immunology* 5:3–11, 1993; Hermann et al., *Immunology* 5:33–39, 1993; Bhardwaj et al., *J. Expt. Med.* 178:633–642, 1993; and Kalland et al., *Med. Oncol. & Tumor Pharmacother.,* 10:37–47, 1993. In particular, various investigators have suggested that Staphylococcal enterotoxin proteins are useful for treating tumors, including Newell et al., *Proc. Natl. Acad. Sci. USA* 88:1074–1078, 1991; Kalland et al., PCT Application No. WO 91/04053, published Apr. 4, 1991; Dohlstein et al., *Proc. Natl. Acad. Sci. USA* 88:9287–9291, 1991; Hedlund et al., *Cancer Immunol. Immunother.* 36:89–93, 1993; Lando et al., *Cancer Immunol. Immunother.* 36:223–228, 1993; Lukacs et al., *J. Exp. Med.* 178:343–348, 1993; Ochi et al., *J. Immunol.* 151:3180–3186, 1993; and Terman et al., PCT Application No. WO 93/24136, published Dec. 9, 1993. These investigators, however, have only disclosed the use of bacterial enterotoxin proteins themselves. The use of bacterial enterotoxin protein has the major disadvantage of being toxic to the recipient of the protein.

Thus, there is a need for a product and process that allows for the treatment of disease using bacterial enterotoxins in a non-toxic manner.

SUMMARY

Traditional pharmaceutical reagents used to treat cancer, infectious diseases and diseases caused by immunological disorders often have harmful side effects. In addition, such reagents can be unpredictable (e.g., treatment of cancer, vaccination against infectious agents). For example, chemotherapy and radiotherapy often cause extensive normal tissue damage during the process of treating cancerous tissue. In addition, vaccine treatments for the prevention or cure of infectious diseases are often ineffective because adjuvants useful in vaccine therapy are toxic to an animal.

The present invention is particularly advantageous in that it provides an effective therapeutic composition that enables the safe treatment of an animal with a reagent that is a potentially toxic an immunogenic protein. Upon delivery, expression of acid molecules contained in the therapeutic composition result in localized production of an effective but non-toxic amount of encoded proteins that may be toxic at concentrations that would be required if the encoded proteins were administered directly. The therapeutic compositions of the present invention can provide long term expression of the encoded proteins at a site in an animal. Such long term expression allows for the maintenance of an effective, but non-toxic, dose of the encoded protein to treat a disease and limits the frequency of administration of the therapeutic composition needed to treat an animal. In addition, because of the lack of toxicity, therapeutic compositions of the present invention can be used in repeated treatments.

BRIEF DESCRIPTION OF THE FIGURES

FIG. **1** illustrates the expression of superantigen-encoding DNA plasmids in mammalian cells.